Review Articles

The effect of thyroid hormone on bone metabolism and osteoporosis

Annie W. C. Kung

Abstract

Thyrotoxicosis has long been known to accelerate bone turnover and thus increase the risk for developing osteoporosis, especially in peri- and postmenopausal women. Increasingly sophisticated tests of thyroid function have indicated that minor degrees of hyperthyroidism are common in patients taking thyroxine (T4) therapy. Recent reports have suggested that women taking TSH-suppressive doses of T4 have reduced bone density. An overview of the effects of thyroid hormone on bone metabolism is presented. The use of sensitive TSH assays can now permit extremely accurate titration of the T4 dosage and should obviate the potential side effects of excessive therapy that results in iatrogenic subclinical thyrotoxicosis.

Keywords: Thyroid hormone; Osteoporosis

Introduction

Thyroid hormone is essential for normal bone maturation in utero and in early life, as hypothyroid infants show features of delayed ossification at epiphyseal centres and children with hypothyroidism have stunted growth and short stature.[1] In contrast, hyperthyroidism in childhood may accelerate linear growth and bone maturation.[2] In adults, recent evidence shows that an excess of thyroid hormones affects the remodelling system in cortical and trabecular bone and may contribute to the development of osteoporosis.

Cellular mechanism of thyroid hormone

Thyroid hormone increases calcium release from fetal rat long bone cultures, and increases osteoclast number and activity.[3] In vivo, thyroid hormone also stimulates osteoblast activity.[4,5] T3 receptor has been demonstrated in osteoblasts[6] but not osteoclasts, suggesting that increased osteoclast activity in bone cultures with T3 treatment is secondary to osteoblast activation.

Bone remodelling normally consists of cyclical erosion and repair of resorptive cavities on bone surface. The bone balance depends on the frequency with which the new cycles are initiated by the event of activation and the focal balance in each remodelling site. The latter depends on the depth of the resorption cavity and the thickness of new bone deposited within the cavity by the osteoblasts, or wall thickness of the bone structure units. In hyperthyroidism the activation frequency is increased and the mineralization time is shortened, resulting in uncoupled bone resorption and decreased mean wall thickness.[7] Conversely, in hypothyroidism, activation frequencies are reduced and the phrase of the remodelling cycle are markedly prolonged. The final resorption depth is reduced whereas the mean wall thickness is increased. The final result is little change in the bone mass.

Thyroid hormone and calcium metabolism

Serum calcium level tends to be high in hyperthy-

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong
Annie W. C. Kung, MD, MRCP(UK)
Correspondence to: Dr Annie W. C. Kung

roidism due to accelerated bone resorption. In a carefully controlled study, the prevalence of hypercalcemia is around 8.5%.[8] The degree of hypercalcemia is usually mild and is just an incidental finding. Increases in serum calcium together with accelerated bone turnover suppress $1,25(OH)_2D_3$ synthesis[9] and inhibit parathyroid hormone release.[10] These together with an increased intestinal motility reduce intestinal calcium absorption. Urinary calcium excretion is also increased in hyperthyroidism. These abnormalities usually revert to normal after treatment.

Bone markers in thyroid diseases

Increased serum or urine markers for bone turnover are observed in hyperthyroidism and the converse was seen in hypothyroidism. These markers include serum alkaline phosphatase (an enzyme produced by osteoblasts),[11] serum osteocalcin (bone GLA protein, a non-collagenous bone matrix protein synthesized by osteoblast),[12] urinary hydroxyproline[13] and 3-hydroxy-pyridinium derivatives (pyridinoline and deoxypyridinoline collagen fibres released during bone resorption)[14]. Increased urinary hydroxyproline[15] and pyridinoline[14] excretion have been reported in patients with low serum TSH levels or on exogenous T4 therapy without clinical signs and symptoms of thyrotoxicosis.

Bone mass in thyrotoxicosis

Although changes in the skeleton of patients with thyrotoxicosis were described as early as 1891, clinical manifestations of bone lesions are uncommon. The incidence of bone changes ranged from 3.5 to 50%,[16] depending on the methodology and criteria used to define demineralization. Using noninvasive bone densitometric techniques, a number of studies have demonstrated that endogenous thyrotoxicosis due to either Graves' disease, toxic adenoma or multinodular goitre is associated with loss of bone mineral content (BMC) at multiple sites in the skeleton. Thyrotoxicosis reduces the amount of both cortical and trabecular bone, with bone loss occurring more severe in peri- and postmenopausal women.[16-18] However, young patients also have lower BMC when compared with age- and sex-matched controls.[19] Some workers observed a significant correlation between the degree of bone turnover with thyroid activity[5] while others found no relation to the duration or the degree of hyperthyroidism.[19]

Is thyrotoxic bone loss permanent or can it be restored? Krolner et al[20] found a reduction of BMC of 12.6% in thyrotoxicosis and a gain of 3.6% after one year of treatment, and Bayley et al.[21] reported a 12.9% increase in total body calcium two years after treatment of thyrotoxicosis. The restoration of bone mass after successful treatment of hyperthyroidism is believed to be related to the prolonged effect of increased bone formation associated with thyrotoxicosis. Whether this degree of bone loss is clinically significant is subject to dispute. Solomon and Burman[22] recently reported that the prevalence of all types of fractures in subjects who have a previous history of thyroid disease is not different from controls but patients with a history of thyrotoxicosis have their first fracture occurring at a younger age. Further longitudinal studies are required to examine the effect or potential risks of endogenous thyrotoxicosis on bone.

Bone mass and thyroxine therapy

With the availability of sensitive TSH assays, it is now possible to determine whether the replacement dose of T4 in the treatment of primary hypothyroidism is excessive. Long term T4 therapy that aims at maintaining euthyroidism with TSH levels in the normal range has been showed to be associated with a small decrement in vertebral and femoral bone density in both pre- and postmenopausal women.[23] Bone loss in the hip and wrists was also observed in premenopausal women on physiologic dosage of T4 replacement therapy, with the degree of bone loss at the femoral neck region negatively correlated with the serum thyroid hormone levels.[24] As for patients with non-toxic goitres and thyroid cancer who require life-long T4 suppressive therapy to suppress TSH secretion, bone loss is observed in both pre- and postmenopausal women. Table 1 summarizes the studies performed on patients taking suppressive doses of T4. Most of the studies reported evidence of bone loss, with estrogen deprivation in the postmenopausal women having a greater degree of loss. However, not all workers agree that T4 treatment would result in bone loss. A few studies showed that exogenous T4 therapy did not have a significant effect on bone mineral density and hence on risk of osteoporosis.[31-33] The reasons for the difference in observation are unclear. Whether this could be related to the dietary calcium and vitamin D intake, the amount of sunlight exposure and physical activity remains to be elucidated. It has to be noted that dietary calcium intake is generally much lower in Asians than Caucasians and this may contribute an additional risk for developing bone loss during T4 therapy.

The question of adjunctive therapy to prevent rapid bone loss during T4 therapy arises, especially in postmenopausal women and older individuals who present with symptomatic or severe bone loss. This question is difficult to address in view of lack of consensus regarding the pathopharmacology of T4

Table 1. Bone mineral density in patients on T4 suppression therapy

Author	Mean dose of L-T4 (mg/day)	Mean serum T4 (μg/dl)	Mean duration of treatment (years)	Method of detection*	Menopausal status	Region of Study	Reduction in BMD
Rose *et al.*, 25	0.171	13.5	>5	DPA	Premenopausal	Forearm	9%
Paul *et al.*, 26	0.175	10.4	>5	DPA	Premenopausal	Femoral neck Trochanter Lumbar spine	12.8% 10% NS
Diamond *et al.*, 27	816[a]	156[b]	10.7	DPA	Premenopausal	Femoral neck Forearm Lumbar spine	11% NS NS
	337[a]	165[b]	5.9	DPA	Postmenopausal	Femoral neck Forearm Lumbar spine	23% 11% 16%
Lehmke *et al.*, 28	0.201	195[b]	5.0	CT + SPA	Premenopausal	Calcanus Radius mildshaft Lumbar Spine	NS NS NS
Taelman *et al.*, 29	0.089	2.4[c]	5.8	SPA	Premenopausal	Radius	5%
	0.100	2.5[c]	>10	SPA	Postmenopausal	Radius	20%
					Postmenopausal	Calcanus Radius midshaft Lumbar spine	22% 14.8% NS
Kung *et al.*, 30	0.179	177[b]	12	DEXA	Postmenopausal	Femur Ward's triangle Lumbar spine	14.3% 16.7% 14.2%
Franklyn *et al.*, 31	0.191	24.5[d]	7.9	DEXA	Pre- and Postmenopausal	Femur Ward's triangle Lumbar spine	NS NS NS
Ribot *et al.*, 32	0.154	17.3[d]	>2	DPA	Pre-and Postmenopausal	Lumbar spine	NS
Toh & Brown, 33	0.131	7.9	3.0	SPA	Male	Distal radius	NS

* DPA, dual-photon absortiometry; CT, computed tomography; SPA, single-photon absortiometry; DEXA, dual-energy x-ray absorptiometry
a Cumulative dose (mg)
b Total T4 (nmol/l)
c Total T3 (nmol/l)
d Free T4 (pmol/l)

induced bone loss. For patients who require replacement therapy for treating hypothyroidism, sensitive TSH assays allow accurate titration of the T4 dosage to avoid over-treatment.[34] This will also help to avoid the other undesirable and deleterious side effects of increased tissue catabolism and increased cardiac load. Obviously, it must also be remembered that there may be important consequences of minor degrees of hypothyroidism arising from undertreatment with T4 with respect to the influences on circulating lipids and hence ischaemic heart disease risk. For those with non-toxic goitre and thyroid cancer who require suppressive therapy, controversy still persists regarding the dosage of T4 to achieve the serum thyroid hormone and the degree of TSH suppression. As for subjects with endogenous thyrotoxicosis, adequate treatment to avoid prolonged period of hyperthyroidism and multiple relapses is mandatory. So far, therapeutic intervention for T4 induced bone loss is still debatable. Further studies of antiresorptive therapy are required before any recommendation is to be given related to patients on long term T4 therapy.

Conclusion

Thyroid hormone increases bone turnover with bone resorption exceeding formation. Physicians treating perimenopausal and postmenopausal women who are at increased risk of osteoporosis should be aware

of the additional risk of bone loss associated with hyperthyroidism or thyroxine therapy. Careful monitoring of thyroid status is necessary in patients receiving thyroxine replacement therapy to avoid over-treatment. Biochemical monitoring of bone markers in conjunction with densitometric studies may be necessary in individuals who have an increased risk of fracture.

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